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Drug utilization pattern and predictors of costs among patients with type II diabetes in Palestine

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ABSTRACT

This study aims to evaluate drug utilization pattern, assess type II diabetes costs and their relationship with patient characteristics, drug utilization pattern, self–care management, and glycemic control. An observational follow–up study conducted for 6 months among 79 type II diabetes patients, randomly selected at a tertiary care center in Ramallah, Palestine. Data on patient characteristics, drug utilization pattern, self–care management and glycemic control were collected from personal interview and medical records review. Data on costs was obtained from personal interview in each visit. Statistical Package for Social Sciences (SPSS v 16.0) was used to perform a descriptive, univariate, and multivariate analysis. The most common prescribed medications were Biguanides, followed by Insulin. Approximately 59.5% of the participants received Statins, 49.4% of them received Angiotensin–Converting Enzyme Inhibitors, 16.5% received oral hypoglycemic drugs, 17.7% received Insulin, and 59.5% were on the combination treatment of oral hypoglycemic drugs and Insulin. The mean ± SD medications number was 4.7 ± 2.2. The mean ± SD age of the participants was 55.9 ± 8.4 years old. More than half of the participants were males (57.0%). The estimated type II diabetes health care cost per 6 months of follow–up incurred by patients and family members was Israeli Shekel 24,000 (US Dollar 6,480). Approximately 47.3% of the participants followed a diabetic meal plan, 60.8% participated in physical exercise, 23.0% tested their blood glucose level at home, and 78.1% were considered adherent with the Eight–Item Morisky Medication Adherence Scale (MMAS–8) score ≥6. While only 21.9% had glycated hemoglobin (HbA1c) level ≤7%. The medications number and Angiotensin–Converting Enzyme Inhibitors were significantly related to health care cost. Type II diabetes costs were not significantly related to self–care management and good glycemic control. This study reflects the need for a more rational prescription mode in line with the patients' health status, and provides a useful platform for further pharmaco–economic research, meanwhile in reducing the costs incurred by patients and family members, whereas it is obvious that the participants were low–income patients.

Keywords: Self–care management, Drug utilization pattern, Cost, Palestine

INTRODUCTION

Diabetes is a common health problem pertains medical consequences that are translated into economic and social consequences on individuals, national health care providers and societies (1). The worldwide diabetes prevalence was estimated to be 6.4% in 2010 among adults aged 20 – 79 years old and will increase to 7.7% by 2030 (2). The estimated worldwide health care expenditure on diabetes will be US Dollar 396 billion by 2025 (3). The developing countries accounted for the largest share of this burden with 75% of these estimates which could be attributed to aging population, unhealthy diet, obesity, increasing urbanization, sedentary lifestyle, and rapid social changes (3-6). The majority of clinical studies addressing type II diabetes characterization focused on developed countries. Meanwhile, the Arab region in general and Palestine in particular lack a holistic research addressing type II diabetes management and health outcomes that requires multi–modal and/or diverse health care resources, along with effective health care system collaboration (7, 8).

The glycemic control benefits are evident. It was reported that every percentage point drop in the glycated hemoglobin (HbA1c) level, will result in reducing the micro–vascular diabetic complications risk by 40% (9). In contrast, patients with diabetic complications have poor glycemic control (HbA1c >7%), higher blood pressure, higher serum cholesterol and triglycerides concentrations (10, 11). Most of the diabetes health care cost is attributed to managing diabetic complications especially when hospitalization and inpatient health care is needed. Moreover, transportation and medication high costs were found to have a significant relationship with patient self–care management. Likewise, elevated health care cost was a major factor related to poor glycemic control (12). In conjunction, patients are expected to play a major role in order to achieve good glycemic control, which is represented by self–care management that is an essential component of the World Health Organization (WHO) and the Palestinian guidelines for type II diabetes management (13, 14).

Glycemic control is believed to be influenced by factors beyond the traditional socio–demographic and clinical characteristics. The majority of type II diabetes patients require a long–term administration of oral hypoglycemic drugs, to ensure good glycemic control (10). In the USA, 57% of type II diabetes patients were treated with a mono–therapy of oral hypoglycemic drugs, only 12% had a combination treatment of oral hypoglycemic drugs and Insulin, 8.6% of patients received Insulin, while 15% neither took Insulin nor oral hypoglycemic drugs (15). This suggests that there is a complex model of socio–demographic, clinical characteristics, drug utilization pattern, self–care management, and glycemic control that are related to costs.

The WHO has regulated the foundations for diabetes management, and recommended all ministries of health registered in the WHO to implement its directions regarding early and effective diabetes management and diagnosis, and for patients to get an ideal health care. Costs and effectiveness of diabetes health care are a matter of foremost consideration. Efficient resources utilization is required. Several studies were carried out in Palestine about diabetes. Unfortunately, none of these studies assess the relationship between factors such as drug utilization pattern and costs. The oral hypoglycemic drugs used to treat type II diabetes are Insulin stimulators; they stimulate Insulin secretion by β–cells, which in turn are subdivided into Sulphonylureas and Non–Sulphonylureas such as Glibenclamide and Repaglinide, respectively. Insulin sensitizers increase Insulin sensitivity and are subdivided into Biguanides (Metformin) and Thiazolidinediones. The available anti–diabetic agents in the Palestinian Drug Formulary are Insulin, Glibenclamide, and Metformin as recommended by WHO (16-19).

This study was conducted among Palestinian type II diabetes patients in order to evaluate drug utilization pattern of different existing drug therapies, and assess type II diabetes costs and their relationship with patient characteristics, drug utilization pattern, self–care management, and glycemic control. The scarcity of research and data on costs incurred by type II diabetes patients and glycemic control in Palestine highlights the importance of determining the expenditures borne by patients and family members and provides decision makers with necessary information to further aid developing personalized diabetes management and control strategies.

METHODS

Study design

This was an observational follow–up study conducted for 6 months among Palestinian type II diabetes patients. The study adopted the prevalence–based approach, which is useful for measuring the economic burden of a disease for a given time period. In the patient perspective, all costs incurred by patients and family members are included (20, 21). Costs on the patients and the family members were estimated in this study based on the co–payments for insured patients and/or fees for uninsured patients, and production losses. The study used 2 data sources. One data source was a set of socio–demographic and health information section, cost diary, and self–care management scale which were conducted via personal interview. The other data source was the medical records, and co–payment and/or fees lists (22).

Participants

This study employed patients who met the sampling criteria from an accessible population who visited the National Center for Chronic Diseases and Dermatology regularly and continuously in Ramallah, Palestine. A tertiary care center affiliated to the Palestinian Ministry of Health that consists of several specialized sections, including diabetes, which is a comprehensive and integrated department serving diabetes patients who were insured under the government health insurance.

The target population was 1200 type II diabetes patients. A minimum sample size is calculated by Daniel formula based on that there is no previous publications about good glycemic control among Palestinian diabetes patients and maximum good glycemic control assumption rate in Palestine to be 50%. Therefore, the total sample size was 292. However, total target population is less than 10000, so adjusted sample size was calculated from Daniel formula and an estimated sample of 235 patients is generated. The researcher recruited 247 patients in order to minimize erroneous results and increase the study reliability. However, the minimum sample size was re–estimated to enroll minimum 20% of calculated sample for an–observational follow–up study to avoid bias sources such as loss of individuals to follow–up during the study (23, 24). Thus, a sample of 79 patients was identified by simple random sampling.

The study included: 1) patients diagnosed with type II diabetes; 2) with available medical records; 3) received ongoing anti–diabetic treatment; 4) currently under active diabetes health care in the center within the previous one year, and 5) willing to participate in the study without physical and/or mental conditions that could interfere with their ability to complete data collection requirements.

Data collection

This study was conducted at the first 6 months in a year, and was approved by MARA University of Technology's Faculty of Pharmacy Postgraduate Academic Committee and Research Management Institute and from the Palestinian Ministry of Health. A personal interview was held to collect data concerning age, gender, occupation, additional chronic diseases, body mass index, smoking status, and anti–diabetic treatment modalities. Participants were asked about their weight and height to calculate their body mass index. Weight and height were measured for participants who cannot remember their weight and height while they are wearing light clothes and taking the shoes off. Body mass index was calculated as weight in kilograms divided by height in meter squared. Participants and researcher were required to record resource use in a detailed way to allow costs calculation by multiplication with unit prices and/or unit costs. During the follow–up time frame, each participant attended personal interview at every visit by using cost diary which is used for covering each visit, and as a tool contributing to assess costs of different kinds. Follow–up participants were required to record information concerning cost analysis that cannot be obtained from the medical and financial records (25, 26).

Direct medical costs are an impact of diabetes health care on the health care services use such as the general practice visits, specialist care, lab tests, and unit prices of medications doses (27). The cost diary's contribution in the direct medical costs measurement is through the visits number via personal interview at each visit to the center; finding out who incurs the costs, whether the participant or any of his/her family members, friends, or others, and thus the overall distribution costs; and medical service/s received and thus confirmed or denied copayments/fees payment (28, 29). Data concerning direct non–medical costs represented by transportation ways and costs was collected. The participants were asked about whether his/her visit was accompanied by someone or alone, and with this part a complete calculation of the total transportation costs per visit according to the transportation mode used to arrive at the center could be made (30, 31). Time loss costs refer to calculating the number of days/hours absent from paid and/or unpaid work and days lost from housekeeping and other daily activities mentioned by the participants during each visit (21, 32, 33). Based on their occupation, the participants were asked about number of days and/or hours that he/she took as leave, seeking to go to the clinic. The same thing applied to employed persons accompanying the participant in order to be able to estimate time lost costs per visit. Hence, total time loss costs during the follow–up period were calculated to get a complete picture of work absence/normal activity lost days/hours of the participants. Furthermore, the participant was directed to indicate the arrival time to the clinic, distance traveled and time needed to arrive at the center. Health care cost was estimated by collecting costs account for the total direct medical costs; as well as total direct non–medical costs and total time loss costs.Self–care management dimensions included diet, physical exercise, testing blood glucose, and medication adherence. Medication adherence was measured using the Eight–Item Morisky Medication Adherence Scale (MMAS–8) developed by Professor Morisky (34, 35). This scale consisted of eight items. The first seven items are yes/no questions while last eighth question is answered on a five point Likert scale. Eight scores from the highest scores of MMAS–8, so scores can range from zero to eight. One score is given for each "No" answer except for question number five where one score is given for "Yes" answer. In the eighth question, zero scores are given if the answer is ticked on "all the time" item, in contrast, to "never/rarely" answer where one score is given. Therefore, the total MMAS–8 score is the sum–up of the scores for the eight items. All available HbA1c last readings and all the prescribed medications were abstracted from medical records by medical records checklist (36). Participants' responses and medical records were treated with confidentiality.

Operational definitions

Patient characteristics were categorized as socio–demographic and clinical characteristics. Patient socio–demographic characteristics included age, gender, and occupation. Whereas, the clinical characteristics included the presence of additional chronic diseases, and cardiovascular diseases risk factors that included body mass index and smoking status. Additional chronic diseases included diabetic complications and non–diabetic comorbidities, and additional chronic diseases number. Body mass index was categorized as normal if body mass index was <25 kg/m², overweight if body mass index was 25 – 29.9 kg/m², and obese if body mass index was ≥30 kg/m² (37, 38). Medication profile consisted of available anti–diabetic agents in the Palestinian Drug Formulary, antihypertensive medications, Statins, and Aspirin. In addition, anti–diabetic treatment modalities, Insulin treatment regimen, and a medications number were the main variables used for assessing drug utilization pattern. A medications number are the number of different medications taken on a daily basis (39, 40). Table 1 shows categories of acquired data concerning medication treatment.

Table (1): *Categories of Medication Profile*

Item	Category
Metformin	Yes/No
Glibenclamide	Yes/No
Insulin	Yes/No
Antihypertensive • ACEI • Others	 Yes/No Yes/No
Statins	Yes/No
Aspirin	Yes/No
Anti–diabetic treatment modalities • Oral hypoglycemic drugs • Insulin • Combined oral hypoglycemic drugs and Insulin	 Yes/No Yes/No Yes/No
Insulin treatment regimen	Insulin Insulin + Metformin Insulin + Metformin Insulin + Metformin + Sulphonylurea
Medications number	≤3 4 – 6 ≥7

Abbreviation: ACEI Angiotensin–Converting Enzyme Inhibitors.

Follow a diabetic meal plan as recommended by the dieticians for 3 days or more in the previous 7 days means that the participants followed an eating plan as recommended by the dieticians. Participants who reported that they walked 3 days or more in the previous 7 days were considered as being engaged, at least 30 minutes in physical exercise. Self–blood glucose monitoring was defined for participants who stated that they performed home glucose monitoring for 5 days or more in the previous 7 days. The MMAS–8 score <6 reflected medication non–adherence, while MMAS–8 score ≥6 reflected medication adherence. (41, 42). Glycemic control was analyzed by determining the proportion of patients with good glycemic control. Good glycemic control refers to follow–up participants who achieved HbA1c level ≤7% (43).

Statistical analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS v 16.0). Mean ± SD health care cost was calculated for subgroups of participants based on categorical variables related to patient characteristics and medication profile. Intergroup differences in health care cost were assessed for statistical significance using multiple linear regressions. Binary logistic regressions followed by multiple logistic regressions were conducted to determine type II diabetes costs that are related to self–care management and good glycemic control. A *P* value <0.05 was considered statistically significant.

RESULTS

Participants' characteristics

The study demonstrated that the mean ± SD age was 56 ± 8.5 (median = 56; Q1 – Q3: 52 – 63). The age category of 48 – 57 accounted for the highest percentage (39.2%). More than half of the participants were males (57.0%). Unemployed participants divested the highest proportion (35.4%). The mean ± SD additional chronic diseases number was 3.3 ± 2.5 (median = 3; Q1 – Q3: 1 – 5). The majority of the participants had diabetic complications (72.2%), and non–diabetic comorbidities were found among 68.4% of the participants. Less than half of the participants were obese (45.6%), and more than one–third of them were smokers (36.1%).

Drug utilization pattern

Metformin was the most frequently prescribed (78.5%), followed by Insulin (75.9%). About 48.1% of the participants were on a mixture of Soluble and Isophane Insulin. Statins ranked first among medications for comorbidities (59.5%), while Angiotensin–Converting Enzyme Inhibitors (ACEI) and Aspirin ranked second (49.4%) and third (45.6%), respectively among medications for comorbidities. Details on all prescribed medications are summarized in Table 2. Combined oral hypoglycemic drugs can be seen (i.e. Sulphonylureas + Metformin). Only 17.7% of the participants received Insulin, about 20.3% was receiving oral hypoglycemic drugs, and more than half of the participants received combination treatment with oral hypoglycemic drugs and Insulin (59.5%). In addition, the high percentage of Insulin includes participants who have been prescribed Insulin or in combination with oral hypoglycemic drugs (Table 3). The mean ± SD different medications number taken on a daily basis was 4.7 ± 2.2 (median = 5; Q1 – Q3: 3 – 6). More than half of the participants took 4 to 6 medications on a regular basis (53.2%).

Table(2): Prescription Pattern of Drugs (N = 79)

Drug Category	Frequency (%)
Metformin	62 (78.5)
Sulphonylureas	15 (19.0)
Sulphonylureas + Metformin	7 (8.9)
Insulin Insulin Isophane Human Soluble Insulin Human Soluble + Isophane Insulin	60 (75.9) 11 (13.9) 11 (13.9) 38 (48.1)
ACEI	39 (49.4)
Aspirin	36 (45.6)
Beta Blockers	17 (21.5)
Calcium Channel Blockers	23 (29.1)
Angiotensin–II Receptor Blocker	4 (5.1)
Diuretics	19 (24.1)
Statins	47 (59.5)
Antibiotics	3 (3.8)
Hematinic, multivitamins	15 (19.0)
Omeprazole, Ranitidine	13 (16.5)
Antidepressants	15 (19.0)
Anticoagulants	7 (8.9)
Angina Pectoris medications	5 (6.3)

Abbreviations: ACEI Angiotensin–Converting Enzyme Inhibitors.

Table(3): Insulin Treatment Regimen (N = 60)

Treatment Type	Frequency (%)
Insulin	14 (23.3)
Insulin + Metformin	39 (65.0)
Insulin + Sulphonylureas	1 (1.7)
Insulin + Metformin + Sulphonylureas	6 (10.0)

Type II diabetes costs

The estimated health care cost incurred by the participants and family members was Israeli Shekel 24,000 (US Dollar 6,480) per 6 months of follow–up. Time loss costs accounted the largest share (60.4%); about 25.2% was direct medical costs and 14.4% was direct non–medical costs. Medication costs accounted for 95.5% of the total direct medical costs and 24.1% of health care cost, respectively, while a percentage of lab tests costs did not exceed 4.5% of the total direct medical costs and 1.1% of health care cost, respectively. The lowest health care cost was found among the age group of 28 – 37 years (mean ± SD = 283.9 ± 101) while the age group of 48 – 57 years acquired the highest health care cost (mean ± SD = 313 ± 180). The mean ± SD health care cost for the male participants was 308 ± 183, which was found to be higher than the same for female participants which was 299.7 ± 114.4. In addition, the highest health care cost was found for those who stated that they were employed (mean ± SD = 340.2 ± 195). There was a significant difference in health care cost among participants with different additional chronic diseases numbers. The highest health care cost found for the group of participants with another 1 additional chronic disease (Mean ± SD = 412.2 ± 210.9). A significant difference in health care cost was found among participants who received ACEI as antihypertensive medication. Subsequently, receiving ACEI was significantly related to health care cost. Furthermore, health care cost was found to increase significantly and steadily with an increasing medications number. The mean ± SD health care cost for participants with a number of medications 3 or less was 230.2 ± 145.6, while the same for those with the number of medications 7 or more was 386.6 ± 163.7 (Table 4).

Table (4): Health Care Cost for Different Categories (ILS[a] at 2014 Prices) (N = 79)

Variable	Frequency (%)	Health Care Cost Mean ± SD	P–Value
Age category			
28 – 37	3 (3.8)	283.9 ± 101.0	0.992
38 – 47	9 (11.4)	310.5 ± 175.3	
48 – 57	31 (39.2)	313.0 ± 180.0	
58 – 67	28 (35.4)	294.7 ± 149.9	
≥68	8 (10.1)	306.3 ± 88.8	
Gender			
Male	45 (57.0)	308.0 ± 183.0	0.816
Female	34 (43.0)	299.7 ± 114.4	
Occupation			
Employed	26 (32.9)	340.2 ± 195.0	0.233
Unemployed	28 (35.4)	267.6 ± 138.5	
Housewife	25 (31.6)	308.5 ± 123.5	
Diabetic complication			
With	57 (72.2)	286.7 ± 127.3	0.106
Without	22 (27.8)	350.3 ± 211.0	
Diabetic complications number			
0	22 (27.8)	350.3 ± 211.0	0.414
1	14 (17.7)	305.6 ± 120.7	
2	17 (21.5)	278.3 ± 108.0	
≥3	26 (32.9)	282.1 ± 144.9	

...continue table (4)

Non–diabetic comorbidities			
With	54 (68.4)	327.7 ± 149.6	0.052
Without	25 (31.6)	254.3 ± 161.8	
Non–diabetic comorbidities number			
0	25 (31.6)	254.3 ± 161.8	0.261
1	15 (19.0)	341.7 ± 178.2	
2	16 (20.3)	331.8 ± 152.8	
≥3	23 (29.1)	315.6 ± 132.3	
Additional chronic diseases number			
0	11 (13.9)	193.4 ± 74.4	0.016
1	12 (15.2)	412.2 ± 210.9	
2	10 (12.7)	299.7 ± 153.5	
3	11 (13.9)	330.4 ± 189.2	
≥4	35 (44.3)	295.6 ± 122.1	
Body mass index			
Normal	8 (10.1)	300.8 ± 100.0	0.977
Overweight	29 (36.7)	314.7 ± 196.6	
Obese	36 (45.6)	312.3 ± 138.7	
Smoking status			
Smoker	27 (34.2)	303.2 ± 166.3	0.721
Non–smoker	46 (58.2)	317.1 ± 156.7	
ACEI			
Yes	39 (49.4)	360.0 ± 173.1	0.01
No	39 (49.4)	249.4 ± 118.1	
Statins			
Yes	47 (59.5)	321.6 ± 154.2	0.246
No	31 (39.2)	279.1 ± 161.2	
Aspirin			
Yes	36 (45.6)	337.6 ± 148.0	0.105
No	43 (54.4)	279.3 ± 161.3	
Insulin duration			0.815
≤5	34 (43.0)	310.1 ± 153.2	
>5 and <10	8 (10.1)	284.9 ± 107.4	
≥10	15 (19.0)	330.2 ± 175.5	
Not taking Insulin	14 (17.7)	278.3 ± 173.5	
Anti–diabetic treatment modalities			
Oral hypoglycemic drugs	16 (20.3)	282.8 ± 160.7	0.616
Insulin	14 (17.7)	289.6 ± 202.2	
Combined oral hypoglycemic drugs and Insulin	47 (59.5)	322.1 ± 141.7	
Anti–diabetic regimen			
Metformin	9 (11.4)	298.8 ± 209.2	0.846
Sulphonylureas + Metformin	7 (8.9)	262.2 ± 73.1	
Insulin	14 (17.7)	289.6 ± 202.2	
Insulin + Metformin	39 (49.4)	322.8 ± 133.0	
Insulin + Metformin + Sulphonylureas	7 (8.9)	339.3 ± 194.5	
Medications number			
≤3	23 (29.1)	230.2 ± 145.6	0.008
4 – 6	42 (53.2)	317.7 ± 145.1	
≥7	14 (17.7)	386.6 ± 163.7	

Abbreviations: ILS Israeli Shekel; *SD* Standard deviation; *ACEI* Angiotensin–Converting Enzyme Inhibitors.
[a]1 Israeli Shekel equals 0.27 US Dollar.

Adjusting covariates using multiple linear regressions found that medications number and receiving ACEI are the variables that were still significantly and independently related to health care cost as shown in Table 5 ($P < 0.05$). The sample multiple correlation coefficients (R) of 2 variables and health care cost was 0.425 and the adjusted R–square was 0.148 ($F(3,74) = 5.441$, $p < 0.05$). Therefore, the medications number and receiving ACEI accounted for 14.8% of the health care cost variance. The largest standardized coefficient (β) was for the medications number, which was 0.261 (Table 5). Thus, the medications number made the strongest unique contribution for explaining health care cost variations.

Table (5): Multiple Linear Regression for Factors Related to Health Care Cost

Variable	Standardized Coefficients (β)	Unstandardized Coefficients (B)	SE	T	P–Value
Chronic diseases number	–0.030	–3.141	11.740	–0.268	0.790
ACEI	–0.259	–81.011	35.649	–2.272	0.026
Medications number	0.261	60.203	27.514	2.188	0.032

Abbreviation: SE Standard error; *ACEI* Angiotensin–Converting Enzyme Inhibitors.

Costs relating to self–care management

About 47.3% of participants followed a diabetic meal plan as recommended by the dietitians. More than half of the participants participated in physical exercise (60.8%), and only 23% of participants used to test their blood–glucose levels at home. Most participants were found to be medication adherent (78.4%), and only 21.6% were non–adherent. Univariate analysis (Table 6) showed that there was a significant difference between participants who followed a diabetic meal plan as recommended by the dieticians and those who did not follow in health care cost and time loss costs. Subsequently, participants who followed the dietitians' diabetic meal plan had a significantly higher health care cost and time loss costs ([O.R = 1.003; 95% C.I of 1.000 – 1.007] and [O.R = 1.004; 95% C.I of 1.000 – 1.008], respectively). However, multivariate analysis (Table 7) showed that there was no significant difference between participants who followed and those who did not follow a diabetic meal plan as recommended by the dieticians in health care cost and time loss costs.

Table (6): Univariate Analysis of Costs Related to Follow a Diabetic Meal Plan

Cost	Cost Mean ± SD or Median [Interquartile Range]	Followed (21.9%)	Did not Follow (78.1%)	Odds Ratio with 95% C.I	P–Value
Health care cost	310.0 ± 151.5	348.8 ± 155.2	275.2 ± 141.1	1.003 (1.000 – 1.007)	0.043
Direct costs	122.4 ± 67.0	132.9 ± 72.6	112.9 ± 61.0	1.005 (0.997 – 1.012)	0.204
Direct medical costs	68.0 [41.5 – 111.8]	70.5 [48.5 – 125.0]	57.0 [39.0 – 109.0]	1.01 (1.00 – 1.02)	0.317
Direct non–medical costs	35.0 [18.0 – 60.0]	45.0 [18.0 – 72.0]	30.0 [18.0 – 60.0]	1.01 (1.00 – 1.02)	0.321
Time loss costs	156.0 [104.0 – 224.7]	202.8 [124.8–280.8]	145.6 [102.2 – 187.2]	1.004 (1.000 – 1.008)	0.008

Abbreviation: SD Standard deviation*; C.I* Confidence interval.

Table (7): Multivariate Analysis of Costs Related to Follow a Diabetic Meal Plan

Cost	Coefficient (β)	S.E	Wald	Odds Ratio with 95% C.I	P–Value
Health care cost	0.004	0.004	1.107	1.004 (0.997–1.011)	0.293
Time loss costs	0.000	0.004	0.019	0.999 (.0991–1.008)	0.890

Abbreviations: S.E Standard error; *C.I* Confidence interval.

Univariate analysis of type II diabetes costs related to physical exercise participation proved that there was no significant difference between participants who participated in physical exercise and those who did not (i.e. either never performed physical exercise or participated in physical exercise but less than 30 minutes per day in the previous 7 days) in type II diabetes costs (Table 8).

Table (8): Univariate Analysis of Costs Related to Physical Exercise Participation

Cost	Cost Mean ± SD or Median [Interquartile Range]	Participated (60.8%)	Did not Participate (39.2%)	Odds Ratio with 95% C.I	P–Value
Heath care cost	299.8 [203.2 – 381.0]	301.4 [213.0 – 381.3]	290 [160.9 – 368.4]	1.001 (0.998 – 1.005)	0.412
Direct costs	122.4 ± 67.0	119.8 ± 61.5	126.5 ± 75.5	0.998 (0.992 – 1.005)	0.673
Direct medical costs	68.0 [41.5 – 111.8]	67.0 [44.0 – 121.0]	69.0 [36.0 – 94.0]	1.003 (0.992 – 1.014)	0.621
Direct non–medical costs	35.0 [18.0 – 60.0]	30.0 [15.0 – 60.0]	40.0 [21.8 – 65.0]	0.993 (0.982 – 1.004)	0.238
Time loss costs	156.0 [104.0 – 224.7]	164.7 [129.9 – 246.0]	135.2 [86.1 – 224.1]	1.002 (0.998 – 1.007)	0.237

Abbreviation: SD Standard deviation; *C.I* Confidence interval.

Univariate analysis (Table 9) showed that there was no significant difference between participants who used to test their blood glucose level at home and those who did not test their blood glucose level at home in type II diabetes costs.

Table (9): Univariate Analysis of Costs Related to Testing Blood Glucose

Cost	Cost Mean ± SD or Median [Interquartile Range]	Yes (23%)	No (77%)	Odds Ratio with 95% C.I	P–Value
Health care cost	299.8 [203.2 – 381.0]	301.4 [203.6 – 333.1]	296.4 [200.7 – 381.3]	0.998 (0.994 – 1.002)	0.379
Direct costs	122.0 ± 67.0	124.3 ± 79.6	121.8 ± 63.5	1.001 (0.993 – 1.009)	0.892
Direct medical costs	68.0 [41.5 – 111.8]	60.0 [32.5 – 114.5]	69.0 [42.5 – 115.0]	0.999 (0.986 – 1.011)	0.846
Direct non–medical costs	35.0 [18.0 – 60.0]	40.0 [19.0 – 72.5]	35.0 [16.5 – 60.0]	1.003 (0.990 – 1.015)	0.674
Time loss costs	156.0 [104.0 – 224.7]	135.2 [109.2 – 200.7]	156.0 [104.0 – 275.6]	1.6 (1.0 – 2.2)	0.268

Abbreviation: SD Standard deviation; *C.I* Confidence interval.

The univariate analysis results of type II diabetes costs related to medication adherence (Table 10) showed a lack of significant difference between medications adherers and non–adherers in type II diabetes costs.

Table (10): Univariate Analysis of Costs Related to Medication Adherence

Cost	Mean ± SD or Median [Interquartile Range]	Adherent (78.4%)	Non–Adherent (21.6%)	Odds Ratio with 95% C.I	P–Value
Health care cost	299.8 [203.2 – 381.0]	301.4 [207.6 – 390.5]	290.6 [186.3 – 362.2]	1.002 (0.998 – 1.006)	0.284
Direct costs	122.4 ± 67.0	127.6 ± 69.1	103.7 ± 56.5	1.01 (1.00 – 1.02)	0.209
Direct medical costs	68.0 [41.5 – 111.8]	69.0 [42.3 – 121.3]	62.0 [37.5 – 87.8]	1.01 (1.00 – 1.02)	0.324
Direct non–medical costs	35.0 [18.0 – 60.0]	38.0[18.0 – 62.5]	21.0 [15.8 – 55.0]	1.01 (1.00 – 1.02)	0.330
Time loss costs	156.0 [104.0 – 224.7]	156.0 [104.0 – 229.0]	156.0 [106.6 – 230.9]	1.002 (0.997 – 1.006)	0.538

Abbreviation: SD Standard deviation*; C.I* Confidence interval.

Costs relating to good glycemic control

The majority of the participants had poor glycemic control (78.1%). Only 21.9% of the participants achieved good glycemic control. The univariate analysis results (Table 11) showed a significant relationship between good glycemic control and factors related to total direct costs, both direct medical and non–medical costs. So, increased total direct costs, both medical and non–medical were significantly related to decreased odds of good glycemic control ([O.R = 0.979, 95% C.I of 0.965 – 0.993] and [O.R = 0.978, 95% C.I of 0.961 –0.996] and [O.R = 0.977, 95% C.I of 0.956 – 0.999] respectively). In the multivariate analysis (Table 12), there was non–significant relationship between good glycemic control and total direct costs, both medical and non–medical costs.

Table (11):Univariate Analysis of Costs Related to Good Glycemic Control

Cost	Cost Mean ± SD or Median [Interquartile Range]	Good Glycemic Control (21.9%)	Poor Glycemic Control (78.1%)	Odds Ratio with 95% C.I	P–Value
Health care cost	297.2 ± 155.0	241.3 ± 125.9	312.9 ± 159.7	0.996 (0.992 – 1.001)	0.108
Total direct costs	119.8 ± 67.9	73.9 ± 36.5	132.7 ± 69.3	0.979 (0.965 – 0.993)	0.004
Direct medical costs	69.0 [41.0 – 109.0]	49.5 [29.6 – 71.3]	70.0 [46.5 – 125.3]	0.978 (0.961 – 0.996)	0.018
Direct non–medical costs	30.0[13.5 – 60.0]	16.5[1.5 – 29.6]	36.0[16.5 – 67.0]	0.977 (0.956 – 0.999)	0.042
Time loss costs	156.0 [94.8 – 218.6]	156.0 [105.8 – 218.4]	156.0 [93.6 – 227.8]	0.999 (0.995 – 1.004)	0.718

Abbreviation: SD Standard deviation*; C.I* Confidence interval.

Table (12): Multivariate Analysis of Costs Related to Good Glycemic Control

Cost	Coefficient (β)	S.E	Wald	Odds Ratio with 95% C.I	P–Value
Total direct costs	–0.02	0.01	3.59	0.98 (0.96 – 1.00)	0.058
Direct medical costs	0.00	0.02	0.00	1.00 (0.97 – 1.03)	0.964

Abbreviations: S.E Standard error; *C.I* Confidence interval.

Discussion

The study found that Metformin was the most frequently prescribed medication, followed by Insulin, and the least was Sulphonylureas, either as mono–therapy or in combination with other oral hypoglycemic drugs. This finding was inconsistent with what is found in other studies (44, 45). Sulphonylureas were the most frequently prescribed oral hypoglycemic drugs in late 1990 (46). However, the prescribing pattern orientation moved toward Metformin as the most frequently prescribed oral anti–diabetic agent, which is consistent with findings reported by other studies (16, 19, 47-49).

Metformin is the first choice to start treating type II diabetes patients along with lifestyle recommendations in accordance to what is recommended by WHO and American Diabetes Association (ADA) to start using Metformin concurrently with lifestyle modification at the diagnosis time due to its effectiveness, low costs, low side effects incidence especially in terms of hypoglycemia, its advantages in the patient's lipid profile improvement, and diabetic complications prevention. It reduces Insulin resistance and might have a positive influence on pancreatic β–cell (50-55). Both Metformin and Sulphonylureas can be used in combination with other oral hypoglycemic drugs or Insulin (14, 51, 55). This study found that Sulphonylureas were prescribed for almost 19% of the participants and in combination with Metformin for 8.9% of the participants. Sulphonylureas remain second main choice and best choice for combination with Metformin as oral anti–diabetic agent regardless of the rapid decrease in their effectiveness over time (56). Therefore, prescription of a combination of Metformin and Sulphonylureas remains a common practice (57).

Different Insulin types were prescribed alone or in combination with oral hypoglycemic drugs of different groups. Failure of oral hypoglycemic drugs results in the Insulin use alone or in combination with oral hypoglycemic drugs. This was reflected in the results of the study shown to include Insulin alone, in addition to Metformin; Sulphonylureas; and Metformin and Sulphonylureas together, which are consistent with findings reported by other studies (8, 58), but with different percentages. The study results proved that there is an increase in Insulin utilization justified by oral hypoglycemic drugs resistance and/or presence of comorbidities (57). The combination of Insulin with Metformin was most commonly prescribed among the participants who were prescribed Insulin. The combination of Insulin with Metformin can cause liver sensitization to the Insulin action which at least may have a synergistic action in blood glucose level control (59). Sulphonylureas use in combination with Insulin can improve the Insulin effectiveness in the type II diabetes management after oral hypoglycemic drugs secondary failure, which can improve blood glucose levels and decrease the need for Insulin (58, 59). The study results have shown that Insulin use in addition to Sulphonylureas and Metformin provides an opportunity to take the Insulin use benefits in combination with oral hypoglycemic drugs (57, 59, 60).

Statins and Aspirin highlight the multiple connotations linked to diabetic complications and non–diabetic comorbidities (56, 61, 62). Many studies supported the fact that type II diabetes patients are at risk of diabetic complications, and cardiovascular diseases were the most common comorbidities found in diabetic patients, in which hypertension was the most common, followed by hyperlipidemia (11, 63, 64). The ACEI role in cardiovascular diseases prevention, suppression of the progressive development of diabetic nephropathy and micro– and macro–vascular diabetic complications with less health care cost and more effectiveness might be a justification for prescribing ACEI as a principal strategy to increase patient’s survival (65, 66). In addition, the study results concerning ACEI prescription reflected what is found in another study (67) which reported that ACEI prescription increased to 72%.

β–blockers prescription rates were the lowest among the prescribed medications for the participants. This reflects a growing concern which tends toward β–blocker underuse due to the fact that suggested β–blockers avoidance especially non–selective because of the probability of masking signs and hypoglycemia symptoms (45, 56). Further analysis of other drugs revealed Aspirin prescription was 45.6%. This could probably due to the fact documented by ADA that Aspirin has the potential to be used as a primary prevention strategy in diabetic patients with cardiovascular diseases risk factors including age 40 years and above, obesity, hypertension, smoking, dyslipidemia, albuminuria, and family history (62, 68).

This study found that Statins were most commonly prescribed medications for additional chronic diseases. High dyslipidemia rates among diabetic patients accounted for high mortality rate due to cardiovascular diseases. Therefore, diabetes is recognized as equivalent to cardiovascular diseases (69). Subsequently, WHO guideline’s recommendation for diabetes management is based on adding Statins in addition to lifestyle modification irrespective of lipid profile for diabetic patients (70). Statins prescription among the participants is justified. However, lack of Statins in every prescription and/or among all the participants might be due to either trial to avoid side effect or drug–drug interactions or participant's lipid profile was normal regardless of physicians' awareness about the WHO guideline. Also, interruption of some medications varieties in the public clinics and centers occasionally and considering additional medications costs might be a reason for not having Statins in every prescription.

Furthermore, Aspirin is effective as secondary prevention in a cardiovascular morbidity and mortality reduction, which has led to considerable interest in identifying Aspirin as an effective mean for reduction of cardiovascular diseases events and mortality in diabetic patients (71). The Aspirin prescription rate was higher in comparison with previous reports which claimed that 13% of diabetic patients were treated with Aspirin as a primary prevention (72, 73).

Consequently, previous studies about the Aspirin prescription in diabetic patients and presence of hypertension and hyperlipidemia among the participants have led to justifying Aspirin prescription as primary and secondary preventions.

This study demonstrated that the health care cost constituted a major part of the patients' household monthly income. Most of the estimated health care cost was contributed by time loss costs. Conversely, few studies have been done for diabetes costs assessment in Palestine, despite the fact that there is an urgent need for such studies because of the delicate position in terms of politics and economy thereto. Worsening of glycemic control can lead to diabetic complications and increased costs. Furthermore, the presence of non–diabetic comorbidities, obesity, and smoking among diabetic patients are potentially making matters worse concerning health care cost, which highlights the importance of improved glycemic control and addressing other risk factors (74, 75). Review of studies on diabetes costs reported that there is a need for studies on health care cost based on socio–demographic and clinical characteristics of diabetic patients in general and Palestine in particular (76, 77). This study tried to add some of what is new into cost assessment areas. The univariate analysis showed that there is no significant healthcare cost difference among the participants' socio–demographic characteristics.

The univariate analysis found that the additional chronic diseases number, ACEI prescription, and the medications number were found to be statistically significant. However, the additional chronic diseases number was excluded in multiple linear regression. This implies the need for addressing the additional chronic diseases prevalence especially hypertension. No laboratory tests were done to confirm the diabetic complications and non–diabetic comorbidities existence; they were detected from both personal interview and medical records review. The health care cost incurred by those with diabetic complications was not substantially higher than those without diabetic complications. Thus, the likelihood that the study failed to capture all diabetic complications types increased. The health care cost on patients with non–diabetic comorbidities was higher than those without non–diabetic comorbidities. However, there is no progressive increase in health care cost with the increased non–diabetic comorbidities number. The health care cost also differs significantly from a medications number and ACEI prescription pattern. Therefore, the results showed that patients with hypertension incurred the highest heath care cost on the grounds that hypertension prevalence was the highest, and on evidence that multiple linear regression models predicted that health care cost on patients who were prescribed ACEI was found to differ significantly.

This study considered type II diabetes costs as factors for self–care management. The univariate analyses showed a significant relationship between health care cost, and time loss costs and follow a diabetic meal plan as recommended by the dieticians. Therefore, participants who incurred high health care cost and time loss costs were more likely to follow a diabetic meal plan as recommended by the dieticians. This enhances the likelihood that diabetic meal plan is a part of the expenses incurred by the Palestinian patients and their family within out of pocket expenditures. Consequently, financial barriers mitigation by providing a diabetic meal plan commensurate with the income level may enhance follow a diabetic meal plan, so that they were taken into account although the multivariate analysis proved a lack of significant relationship between them and following dietician's meal plan. The findings have shown that type II diabetes costs was not significantly related to physical exercise participation, self–blood glucose monitoring, and medication adherence, which are contrary to the vast majority of studies (78-80). Other study reported that high medication cost is the most important reason for medication non–adherence which is contrary to the study findings (81). Furthermore, adequacy of health care cost in relation to patients' income or full health insurance coverage is a key contributor to rising medication adherence rate (82).

Direct and indirect costs related to the treatment regimen and restricted therapy access are the main reasons leading to self–

care management non–adherence in developing countries (83). Other studies stated that low income patients and/or without health insurance coverage were more likely to be medication non–adherent (84, 85). Consequently, copayment pricing set by the Palestinian Ministry of Health and subsequent low medications costs on insured patients might be the main cause for the limited significant relationship between type II diabetes costs and medication adherence, which is considered as a positive point in favor of the Palestinian governmental health insurance system.

The study results and others indicated that good glycemic control has yet to be achieved in Palestine and Arab region (86). An inefficient diabetes health care might be considered as patient and family resources depletion. Thus, the economic burden has not yet been translated into optimum diabetes health care. The univariate analysis on type II diabetes costs related to good glycemic control showed a significant relationship between good glycemic control and direct costs, both direct medical and non–medical costs. The multivariate analysis showed that there were no costs significantly related to good glycemic control. However, they deserve attention due to the clarity of these relationships in multiple studies. Effective diabetes health care had lower direct cost, both direct medical and non–medical costs. This finding is reported to be similar to another study which reported a relationship between improved glycemic control and reduced health care cost (74). Improved glycemic control is significantly related to improving overall health status and health economic benefits (12, 75, 87). Therefore, the Palestinian Ministry of Health must set the user fees in the public health care centers to suit the patients' income, their treatment needs, and accompanied by a glycemic control improvement, which make more favorable effectiveness/cost ratio. The impacts of charges policy have not been studied in Palestine.

The study had four limitations. First, the sample size is small and follow–up period is short. However, this study can form a strong foundation for future studies with a larger follow–up sample size for a longer duration, beside other health care system factors. Second, some patients refused to take part as consent forms had to be signed, or withdrew from the study, due to the Palestinian traditions and customs. So, the researcher had to convince the participants of the study importance and their roles in effective study completion. Third, the researcher put in extra effort to look for more participants than planned so as to avoid some participants' withdrawals. Finally, data collection methods which were simple, practical, inexpensive, and most common may be limited by recall bias, overestimation, healthcare providers themselves such as incomplete medical records, and patient–related factors such as social desirability, and conversation style that might limit the researcher ability to access an accurate answer.

CONCLUSIONS

High oral hypoglycemic drugs frequency was prescribed. Metformin was most commonly prescribed medications. Most of the Insulin preparation contains Human Insulin. More than half of the participants received 4 to 6 different medications on daily basis. Prescription pattern should be reviewed for more rational prescription mode in line with the patients' health status. The study found that health care cost increased as the medications number increased. A significantly lower health care cost was seen in participants receiving ACEI. The patients' proportion with good glycemic control was low. Type II diabetes costs were not significantly related to self–care management and good glycemic control. However, type II diabetes costs are worthy to talk about them as related factors to good glycemic control to provide a useful platform for further pharmaco–economic research in Palestine to put an end of increasing costs and uninterrupted Insulin supply, whereas the participants were low income patients.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest in this manuscript.

REFERENCES

1) Sweileh WM, Zyoud SH, Abu Nab'a RJ, Deleq MI, Enaia MI, Nassar SaM, et al. Influence of patients' disease knowledge and beliefs about medicines on medication adherence: findings from a cross–sectional survey among patients with type 2 diabetes mellitus in Palestine. BMC Public Health 2014; 14(1): 1–8.
2) Shaw JE, Sicree RA and Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87(1): 4–14.
3) International Diabetes Federation 2003. Retrieved from http://www.diabetesatlas.org/ resources/previous-editions.html (Accessed June 6, 2014).
4) Chuang LM, Tsai ST, Huang BY and Tai TY. The status of diabetes control in Asia–a cross–sectional survey of 24317 patients with diabetes mellitus in 1998. Diabet Med 2002; 19(12): 978–85.
5) Echouffo–Tcheugui JB and Dagogo–Jack S. Preventing diabetes mellitus in developing countries. Nat Rev Endocrinol 2012; 8(9): 557–62.
6) Ma S, Cutter J, Tan CE, Chew SK and Tai ES. Associations of diabetes mellitus and ethnicity with mortality in a multiethnic Asian population: data from the 1992 Singapore National Health Survey. Am J Epidemiol 2003; 158(6): 543–52.
7) Husseini A, Abu–Rmeileh NM, Mikki N, Ramahi TM, Ghosh HA, Barghuthi N, et al. Cardiovascular diseases, diabetes mellitus, and cancer in the occupied Palestinian territory. Lancet 2009; 373(9668): 1041–9.
8) Sweileh WM, Sa'ed HZ, Al–Jabi SW and Sawalha AF. Bibliometric analysis of diabetes mellitus research output from Middle Eastern Arab countries during the period (1996–2012). Scientometrics 2014; 101(1): 819–32.
9) Ramachandran A, Ramachandran S, Snehalatha C, Augustine C, Murugesan N, Viswanathan V, et al. Increasing expenditure on health care incurred by diabetic subjects in a developing country: a study from India. Diabetes Care 2007; 30(2): 252–6.
10) Lanham HJ, McDaniel RR, Crabtree BF, Miller WL, Stange KC, Tallia AF, et al. How improving practice relationships among clinicians and nonclinicians can improve quality in primary care. Jt Comm J Qual Patient Saf 2009; 35(9): 457–66.
11) Sweileh WM, Sawalha AF, Zyoud SH, Al–Jabi SW and Tameem EJ. Patterns of anti–hypertensive therapy in diabetic patients with and without reduced renal function. Saudi J Kidney Dis Transpl 2010; 21(4): 652–9.
12) Sweileh WM, Sawalha AF, Salfeete SA, Zyoud SH, Abu–Taha AS, Al–jabi SW, et al. Admission blood glucose level as a potential indicator for short–term mortality and morbidity after myocardial infarction. Int J Diab Dev Ctries 2006; 26(3): 116–21.
13) Ackermann EW and Mitchell GK. An audit of structured diabetes care in a rural general practice. Med J Aust 2006; 185(2): 69–72.

14) Jamous RM, Sweileh WM, Abu Taha AS, Sawalha AF, Zyoud SH and Morisky DE. Adherence and satisfaction with oral hypoglycemic medications: a pilot study in Palestine. Int J Clin Pharm 2011; 33(6): 1028–35.
15) Santos–Longhurst D 2014. Retrieved from http://www.healthline.com/health/type-2-diabetes/statistics#1 (Accessed January 20, 2015).
16) Krentz AJ and Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs 2005; 65(3): 385–411.
17) Palestinian Ministry of Health 2003. Retrieved from http://www.alazhar.edu.ps/Library/ aattachedFile.asp?id_no=0042922 (Accessed February 3, 2012).
18) Woodward M, Lam TH, Barzi F, Patel A, Gu D, Rodgers A, et al. Smoking, quitting, and the risk of cardiovascular disease among women and men in the Asia–Pacific region. Int J Epidemiol 2005; 34(5): 1036–45.
19) Sweileh WM. Contraindications to metformin therapy among patients with type 2 diabetes mellitus. Pharm World Sci 2007; 29(6): 587–92.
20) Drummond MF and McGuire A. Economic Evaluation in Health Care: Merging Theory with Practice. Oxford: Oxford University Press; 2001.
21) Kobelt G. Health Economics: An Introduction to Economic Evaluation. London: Office of Health Economics; 2002.
22) Chang TK, Li YM and Shaw CK. The study of health care accessibility in remote areas of Hualien County after the launching of National Health Insurance Program. Tzu Chi Med J 1998; 10: 201–9.
23) Daniel WW. Biostatistics: Basic Concepts and Methodology for the Health Sciences. New Jersey: John Wiley & Sons; 2010.
24) Palestinian Ministry of Health 2012. Retrieved from http://www.moh.ps/Content/Books /nbcgI6bZxmosmDSuKLtbaawjztq8IwQ5N91Y138fwjS62fZBq9m4Qi_CcymmeY82fpborVA7zMqOQh4bFPeaMB4poPS5svvyLVEIRyeXzfBE8.pdf (Accessed 20 February, 2013).
25) Goossens ME, Rutten–van Molken MP, Vlaeyen JW and van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost–effectiveness research. J Clin Epidemiol 2000; 53(7): 688–95.
26) van der Heijden AA, de Bruijne MC, Feenstra TL, Dekker JM, Baan CA, Bosmans JE, et al. Resource use and costs of type 2 diabetes patients receiving managed or protocolized primary care: a controlled clinical trial. BMC Health Serv Res 2014; 14(1): 1–8.
27) Brouwer W, Rutten F and Koopmanschap M. Economic evaluation in health care – merging theory with practice. New York: Oxford University Press; 2001.
28) Kerkenbush NL. A comparison of self–documentation in diabetics: electronic versus paper diaries. AMIA Annu Symp Proc 2003: 887.
29) Abd. Aziz AM, Yusof FA, Manan MM, Zainal R, Said S, Hj. Hussain S, et al. 2014. Retrieved from https://www.researchgate.net/publication/291639839The_cost_of_diabetes_care_for_ambulatory_patients_in_Malaysian_Ministry_of_Health_facilities (Accessed December 10, 2014).
30) Borges NB, Ferraz MB and Chacra AR. The cost of type 2 diabetes in Brazil: evaluation of a diabetes care centre in the city

of São Paulo, Brazil. Diabetol Metab Syndr 2014; 6(1): 1–10.

31) Hu H, Sawhney M, Shi L, Duan S, Yu Y, Wu Z, et al. A systematic review of the direct economic burden of type 2 diabetes in China. Diabetes Ther 2015; 6(1): 7–16.
32) Hernan WH, Brandle M, Zhang P, Williamson DF, Matulik MJ, Ratner RE, et al. Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program. Diabetes Care 2003; 26(1): 36–47.
33) Williams R 2002. Retrieved from https://www.idf.org/sites/default/files/attachments/article_125_en.pdf (Accessed April 12, 2012).
34) Morisky DE, Ang A, Krousel–Wood M and Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008; 10(5): 348–54.
35) Morisky DE, Green LW and Levine DM. Concurrent and predictive validity of a self–reproted measure of medication adherence. Med Care 1986; 24(1): 67–74.
36) Aday LA. Evaluating the healthcare system: effectiveness, efficiency, and equity. Chicago: Health Administration Press; 2004.
37) Schweizer A, Dejager S and Foley JE. Impact of insulin resistance, body mass index, disease duration, and duration of metformin use on the efficacy of vildagliptin. Diabetes Ther 2012; 3(1): 1–9.
38) World Health Organization 1994. Retrieved from http://apps.who.int/iris/bitstream/10665/116245/1/dsa509.pdf (Accessed 13 June, 2012).
39) Grant RW, Devita NG, Singer DE and Meigs JB. Polypharmacy and medication adherence in patients with type 2 diabetes. Diabetes Care 2003; 26(5): 1408–12.
40) Zyoud SH, Al–Jabi SW, Sweileh WM and Morisky DE. Relationship of treatment satisfaction to medication adherence: findings from a cross–sectional survey among hypertensive patients in Palestine. Health Qual Life Outcomes 2013; 11(191).
41) Ackroyd SA and Wexler DJ. Effectiveness of diabetes interventions in the patient–centered medical home. Curr Diab Rep 2014; 14(3): 471–87.
42) Machado–Alba JE, Moncada–Escobar JC and Gaviria H. Quality and effectiveness of diabetes care for a group of patients in Colombia. Rev Panam Salud Publica 2009; 26(6): 529–35.
43) World Health Organization 2007. Retrieved from http://applications.emro.who.int/docs/EM_RC54_Tech_Disc_1_en.pdf?ua=1 (Accessed 5 November, 2014).
44) Boccuzzi SJ, Wogen J, Fox J, Sung JC, Shah AB and Kim J. Utilization of oral hypoglycemic agents in a drug–insured U.S. population. Diabetes Care 2001; 24(8): 1411–5.
45) Truter I. An investigation into antidiabetic medication prescribing in South Africa. J Clin Pharm Ther 1998; 23(6): 417–22.
46) Xavier D, Naga Rani MA and Srishyla MV. Drug utilisation study of anti–hypertensives and anti–diabetics in an Indian referral hospital. Indian J Pharmacol 1999; 31(3): 241–2.
47) Boyc KS, Yurgin N and Lage MJ. Trends in the prescription of antidiabetic medications in France: evidence from primary care physicians. Adv Ther 2007; 24(4): 803–13.

48) Das P, Das BP, Rauniar GP, Roy RK and Sharma SK. Drug utilization pattern and effectiveness analysis in diabetes mellitus at a tertiary care centre in eastern Nepal. Indian J Physiol Pharmacol 2011; 55(3): 272–80.
49) Johnson JA, Pohar SL, Secnik K, Yurgin N and Hirji Z. Utilization of diabetes medication and cost of testing supplies in Saskatchewan, 2001. BMC Health Serv Res 2006; 6: 159.
50) Alberti KG and Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15(7): 539–53.
51) Brunton L, Chabner B and Knollman B. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw–Hill; 2013.
52) Hogan P, Dall T and Nikolov P. Economic costs of diabetes in the US in 2002. Diabetes Care 2003; 26(3): 917–32.
53) Spada A and Philippe J. Metformin role in the treatment of type 2 diabetes in 2008. Rev Med Suisse 2008; 4(160): 1392–4, 6–7.
54) Stumvoll M, Goldstein BJ and van Haeften TW. Type 2 diabetes: pathogenesis and treatment. Lancet 2008; 371(9631): 2153–6.
55) Tripathi KD. Essentials of Medical Pharmacology. 7th ed. New Delhi: Jaypee Brother’s Medical Publishers (P) Ltd. ; 2013.
56) Kasper DL and Harrison TR. Harrison's Principles of Internal Medicine. New York: McGraw–Hill, Medical Pub. Division; 2005.
57) Vengurlekar S, Shukla P, Patidar P, Bafna R and Jain S. Prescribing pattern of antidiabetic drugs in Indore City Hospital. Indian J Pharm Sci 2008; 70(5): 637–40.
58) Dashputra AV, Badwaik RT, Borkar AS, Date AP and Kalnawat NR. Pattern of antidiabetic drugs used in outpatient and hospitalized patients in a tertiary health institute of Central India. J Cont Med A Dent 2014; 2(3): 48–54.
59) Buse JB. Overview of current therapeutic options in type 2 diabetes. Rationale for combining oral agents with insulin therapy. Diabetes Care 1999; 22 Suppl 3: C65–C70.
60) Scheen AJ, Castillo MJ and Lefebvre PJ. Combination of oral antidiabetic drugs and insulin in the treatment of non–insulin–dependent diabetes. Acta Clin Belg 1993; 48(4): 259–68.
61) Evans JM, MacDonald TM, Leese GP, Ruta DA and Morris AD. Impact of type 1 and type 2 diabetes on patterns and costs of drug prescribing: a population–based study. Diabetes Care 2000; 23(6): 770–4.
62) Sweileh WM, Sawalha AF, Zyoud SH, Al–Jabi SW, Tameem EJ and Shraim NY. Evaluation of antihypertensive therapy in diabetic hypertensive patients: impact of ischemic heart disease. Pharm Pract (Granada) 2009; 7(1): 40–6.
63) Upadhyay DK, Palaian S, Ravi Shankar P, Mishra P and Sah AK. Prescribing pattern in diabetic outpatients in a tertiary care teaching hospital in Nepal. J Clin Diagn Res 2007; 1(4): 248–55.
64) Yurgin N, Secnik K and Lage MJ. Antidiabetic prescriptions and glycemic control in German patients with type 2 diabetes mellitus: a retrospective

database study. Clin Ther 2007; 29(2): 316–25.
65) Campbell HM, Boardman KD, Dodd MA and Raisch DW. Pharmacoeconomic analysis of angiotensin–converting enzyme inhibitors in type 2 diabetes: a Markov model. Ann Pharmacother 2007; 41(7): 1101–10.
66) Satoskar RS, Rege NN and Bhandarkar SD. Pharmacology and Pharmacotherapeutics. 23rd ed. Mumbai: Popular Prakashan; 2013.
67) Schmittdiel JA, Uratsu CS, Fireman BH and Selby JV. The effectiveness of diabetes care management in managed care. Am J Manag Care 2009; 15(5): 295–301.
68) American Diabetes Association. Standards of medical care in diabetes–2007. Diabetes Care 2007; 30 Suppl 1: S4–S41.
69) Bentler SE, Morgan RO, Virnig BA and Wolinsky FD. The association of longitudinal and interpersonal continuity of care with emergency department use, hospitalization, and mortality among medicare beneficiaries. PLoS One 2014; 9(12): 1–18.
70) Eldor R and Raz I. American Diabetes Association indications for statins in diabetes: is there evidence? Diabetes Care 2009; 32 Suppl 2: S384–S91.
71) Antithrombotic Trialists Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta–analysis of individual participant data from randomised trials. The Lancet 2009; 373(9678): 1849–60.
72) Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes. Diabetes Care 2010; 33(6): 1395–402.
73) Ritz E and Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med 1999; 341(15): 1127–33.
74) Gilmer TP, O'Connor PJ, Rush WA, Crain AL, Whitebird RR, Hanson AM, et al. Predictors of health care costs in adults with diabetes. Diabetes Care 2005; 28(1): 59–64.
75) Testa MA and Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double–blind trial. Jama 1998; 280(17): 1490–6.
76) Ettaro L, Songer TJ, Zhang P and Engelgau MM. Cost–of–illness studies in diabetes mellitus. Pharmacoeconomics 2004; 22(3): 149–64.
77) Government of the State of Palestine MoP 2006. Retrieved from http://www.mopad.pna.ps/en/attachments/article/28/The%20Medium-Term%20Development%20Plan%202006%202008.pdf (Accessed April 11, 2013).
78) Lertmaharit S, Kamol–Ratankul P, Sawert H, Jittimanee S and Wangmanee S. Factors associated with compliance among tuberculosis patients in Thailand. J Med Assoc Thai 2005; 88 Suppl 4: S149–S56.
79) Shams MEE and Barakat EAME. Measuring the rate of therapeutic adherence among outpatients with T2DM in Egypt. Saudi Pharm J 2010; 18(4): 225–32.
80) Seo MA and Min SK. Development of a structural model explaining medication compliance of persons with schizophrenia. Yonsei Med J 2005; 46(3): 331–40.
81) García–Pérez LE, Álvarez M, Dilla T, Gil–Guillén V and Orozco–Beltrán D. Adherence to

therapies in patients with type 2 diabetes. Diabetes Ther 2013; 4(2): 175–94.

82) Adisa R, Alutundu MB and Fakeye TO. Factors contributing to nonadherence to oral hypoglycemic medications among ambulatory type 2 diabetes patients in Southwestern Nigeria. Pharm Pract (Granada) 2009;7(3): 163–9.

83) Ohene Buabeng K, Matowe L and Plange–Rhule J. Unaffordable drug prices: the major cause of non–compliance with hypertension medication in Ghana. J Pharm Pharm Sci 2004; 7(3): 350–2.

84) Choi–Kwon S, Kwon SU and Kim JS. Compliance with risk factor modification: early–onset versus late–onset stroke patients. Eur J Neurol 2005; 54(4): 204–11.

85) Mishra P, Hansen EH, Sabroe S and Kafle KK. Socio–economic status and adherence to tuberculosis treatment: a case–control study in a district of Nepal. Int J Tuberc Lung Dis 2005; 9(10): 1134–9.

86) Abdelgadir M, Elbagir M, Eltom A, Eltom M and Berne C. Factors affecting perinatal morbidity and mortality in pregnancies complicated by diabetes mellitus in Sudan. Diabetes Res Clin Pract 2003; 60(1): 41–7.

87) Sweileh WM, Sawalha AF, Zyoud SH, Al–Jabi SW and Shraim NY. Prevalence of reduced renal function among diabetic hypertensive patients. Int J Physiol Pathophysiol Pharmacol 2009; 1(1): 41–7.